REMARKS

Claims 1-26 are pending. Claims 1, 7-8, and 13-26 are rejected, while claims 2-6 and 9-12 are objected to for depending from rejected claims. Claims 13, 14, and 17 have been canceled without prejudice to continued prosecution. Claims 1, 23, and 24 have been amended to recite that the immunostimulatory dosage is about 4,000,000 U/ m^2 per day or less. Support for this amendment can be found throughout the specification, including page 11, lines 16-17. Claims 18-20 have been amended to recite resectable malignant tumor. Support for this amendment can be found throughout the specification, including page 8, lines 28-31. Claims 25 and 26 have been amended to recite that the immunostimulatory dosage is about 1,000,000 U/m^2 per day or less. Support for this amendment can be found throughout the specification, including at page 5, lines 19-22. Reconsideration and allowance of claims 1-12, 15-16, and 18-26 is respectfully requested.

Priority

The Examiner acknowledged Applicant's claim for domestic priority under 35 U.S.C. 119(e). The Examiner asserted "the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. § 112 for claims 10 –12 of this application."

Applicant respectfully traverses. The provisional application indicates that NK lymphocyte cytotoxicity is measured by established protocols, and cites Whiteside et al. (J.Clin. Lab. Anal., 4:102-114 (1990)) for support. See, provisional application at page 9, line 26 through page 10, line 9. Furthermore, the provisional application at page 8, lines 7-9 indicates that the immunostimulatory dosage increases NK lymphocyte cytotoxicity at least about 75% compared to pretreatment NK cytotoxicity levels. Thus, the provisional application supports the claim to priority for claims 10-12.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 17-20 and 24-25 under 35 U.S.C. § 112, second paragraph. The Examiner alleged that it was "not clear how the limitation 'wherein said malignant tumor is

a solid tumor' further limits the scope of claim 1 which is drawn to a method of treating a human patient having 'a resectable malignant tumor'" in claim 17.

Applicant has canceled claim 17 and has amended claims 18-20 to recite resectable malignant tumor. The Examiner is requested to withdraw the rejection of claims 18-20 under 35 U.S.C. § 112, second paragraph.

With respect to claims 24 and 25, the Examiner alleged that it was not clear how the claimed article of manufacture was limited by the recitation that the article of manufacture includes packaging material comprising a label or package insert. The Examiner also asserted that claims 24 and 25 "appear to be duplicates of each other." Applicant respectfully traverses.

Claims 24 and 25 each relate to an article of manufacture comprising packaging material and an α-interferon composition contained within the packaging material, and wherein the packaging material comprises a label or package insert. The labels or package inserts of claims 24 and 25 recite the method by which the α-interferon composition can be used. In claim 24, the label or package insert indicates that administration of an immunostimulatory dosage of the α-interferon composition followed by surgical resection of a malignant tumor can be effective for treating a human patient having the malignant tumor, wherein the immunostimulatory dosage is about 4,000,000 U/m^2 per day or less. In amended claim 25, the label or package insert indicates that administration of an immunostimulatory dosage of the α-interferon composition in conjunction with treating the patient using effective non-surgical medical methodologies can be effective for treating a human patient having the malignant tumor, wherein the immunostimulatory dosage is about 1,000,000 U/m^2 per day or less. Thus, claims 24 and 25 are not duplicates of each other and are limited by the recitation of the method on the package label or insert. Applicant submits that claims 24 and 25 are sufficiently definite under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 13 and 14 under 35 U.S.C. § 112, first paragraph. The Examiner asserted the "specification does not teach why one of skill in the art would expect α-interferon to increase B-lymphocyte activity." This rejection is moot as claims 13-14 have been canceled.

Rejection under 35 U.S.C. § 102

The Examiner rejected claims 24 and 25 under 35 U.S.C. § 102(b) as being anticipated by Ucar et al. (Annals of Allergy, Asthma, and Immunology, 75:377-386, 1995). The Examiner asserted "Ucar et al. disclose three commercial preparations of α-interferon (page 380, 3rd column and Table 4) that is the same as that claimed." Applicant respectfully traverses.

Ucar et al. do not disclose administration of immunostimulatory dosages of α-interferon followed by either surgical resection of a malignant tumor or non-surgical methodologies are effective for treating a human patient having a malignant tumor. It appears that the Examiner did not consider the claim elements relating to the label or package insert. "Differences between an invention and the prior art cited against it cannot be ignored merely because those differences reside in the content of printer matter." In re Gulack, 217 USPQ 401, 403 (Fed. Cir. 1983). This is because describing an element as printed matter reveals nothing about the differences between an invention and the prior art. In re Gulack, 217 USPQ 399, 403 (Fed. Cir. 1983). Instead, "[t]he Patent and Trademark Office (PTO) must consider all claim limitations when determining the patentability of an invention over the prior art." In re Lowry, 32 USPQ2d 1031, 1034 (Fed. Cir. 1994). It is impermissible to dissect out elements of a claim and then declare the remaining portion of the mutilated claim unpatentable. In re Gulack, 217 USPQ 401, 403 (Fed. Cir. 1983).

As a result, proper analysis mandates that a claim be read as a whole. In re Gulack, 217 USPQ 401, 403 (Fed. Cir. 1983). Furthermore, ignoring a claim element simply because the element is unpatentable by itself "is no reason for ignoring it when the claim is directed to the combination." In re Miller, 164 USPQ 46, 49 (CCPA 1969). Indeed, a patentable invention comprises a combination of all new, partly new or all old elements. Rosemount, Inc. v. Beckman Instruments, Inc., 221 USPQ 1, 7 (Fed. Cir. 1984).

Thus, the content of the printed matter portion of the present invention must be considered in determining patentability. In the present case, it has not been established that the content of the printed matter in the claims, i.e., administrating immunostimulatory dosages of α-interferon (4,000,000 U/m^2 or 1,000,000 U/m^2 per day or less) followed by surgical resection or by non-surgical methodologies is effective for treating a malignant tumor, is taught in the cited prior art. Thus, Applicant respectfully submits that the claimed combination is drawn to allowable subject matter.

The Examiner rejected claim 26 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,846,782 (the '782 patent). The Examiner alleged that "U.S. Patent No. 4,846,782 discloses a method comprising administering an immunostimulatory dosage ($2x10^6$ to $5x10^6$ IU/m^2) of an α-interferon composition followed by radiation treatment (column 3, lines 4-6 and lines 45-47) that is the same as that claimed."

Applicant has amended claim 26 to recite that the immunostimulatory dosage is about 1,000,000 U/m^2 per day or less. The '782 patent describes using dosages of $2x10^6$ to $5x10^6$ U/m^2 three times per week, and does not teach that administration of 1,000,000 U/m^2 per day or less of α-interferon, followed by non-surgical methodologies is effective for treating a patient having a malignant tumor.

In view of the above remarks, the Examiner is requested to withdraw the rejections under 35 U.S.C. § 102(b).

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1, 7-8, and 15-22 under 35 U.S.C. § 103 as being unpatentable over Markovic et al. (Int. J. Cancer, 45:788-794, 1990) in view of either Golub et al. (J. Nat. Cancer Inst., 68:703-710, 1982), Toliou et al. (Eur. Urol., 29:252-256, 1996) or Neefe et al. (Cancer Res., 45:874-878, 1985). The Markovic et al. reference was characterized as teaching a "method of treating mice with resectable tumors that have not metastasized" that includes "administering an α-interferon composition for once a day for 5 days prior to the surgical removal of the tumor." The dosages of the Markovic et al. reference were deemed to be immunostimulatory and to increase activity and function of cytotoxic T-lymphocytes. The Examiner asserted that Markovic et al. "do not teach a method for human patients or in specific types of cancers" but that it is "well known in the art that methods first attempted in animal models may be applied to humans." The Golub et al. reference was asserted to teach that α-interferon increases natural killer cytotoxicity against tumor cell targets in melanoma patients. The Toliou et al. reference was alleged to teach that "interferon α2b administered to patients with renal cell carcinoma, prior to surgery, increases the number of natural killer cells within the tumors and increases the activation and cytolytic activity of the natural killer cells." The Neefe et al. reference was viewed as teaching that "α-interferon increase the immune function of

metastatic colon and breast cancer patients." The Examiner asserted that it would have been obvious to combine the teachings of Markovic et al. with either of Golub et al., Toliou et al., or Neefe et al. to make the invention as claimed as the "efficacy of interferon-α lies in its ability to stimulate the immune system against a tumor."

Claim 17 has been canceled. Independent claim 1 has been amended to recite that the immunostimulatory dosage is about 4,000,000 U/ m^2 per day or less without prejudice to continued prosecution. The combination of Markovic et al. with either Golub et al., Toliou et al., or Neefe et al. does not teach or suggest a method of treating a human patient that includes administering about 4,000,000 U/ m^2 per day or less of α-interferon to the patient, then surgically resecting the malignant tumor.

As indicated in MPEP § 2141, "the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;
(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and
(D) Reasonable expectation of success is the standard with which obviousness is determined. Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986)."

While Applicant agrees that many methods tried in animal models may eventually be applied to human patients, Applicant disagrees that the teachings of Markovic et al. provide the legally required reasonable expectation of success in treating human patients by the method of amended claim 1.

Markovic et al. administered α-interferon to mice with primary tumors prior to excision of the tumors. It was observed that tumor-associated mortality was limited and that administration prior to surgery was more effective than administration after surgery. Markovic et al. do not teach or suggest that lower dosages of α-interferon (4,000,000 U/ m^2 per day or less) are useful for treating human patients. Although the doses used by Markovic et al. and the dosages recited in the present claims cannot be directly compared, the trend in Markovic et al. was to use increasing doses of α-interferon. Table 1 of Markovic et al. indicates that increased

amounts of α-interferon increased the percent survival and increased the median survival time of the mice. Administering $2.5x10^4$ U of α-interferon/day to mice resulted in a median survival time of 45 days, whereas administering increased doses ($1.0x10^5$ U/day) resulted in a median survival time of greater than 84 days. See, Table 1 of Markovic et al., page 790. Thus, one of ordinary skill in the art would expect that increasing the dosage of α-interferon would be beneficial. In contrast, the claimed invention relates to use of lower dosages of α-interferon (4,000,000 U/ m^2 per day or less).

Golub et al., Toliou et al., and Neefe et al. do not remedy the deficiencies of Markovic et al. Golub et al. administered α-interferon to patients with metastatic malignant melanoma for 42 consecutive days. Toliou et al. administered interferon-α2b to patients with renal cell carcinoma prior to surgery and evaluated tumor sections for the number of natural killer cells. Toliou et al. indicate that natural killer cell values after interferon administration may be of use for selecting patients for more aggressive therapies or as a way to monitor biotherapies. See, Toliou et al., page 256. Neefe et al. administered recombinant interferon-αA to colon or breast cancer patients and assessed natural killer cell activity and the inhibition of tumor growth. Golub et al., Toliou et al., and Neefe et al. do not teach or suggest that administrating 4,000,000 U/ m^2 per day or less of α-interferon to a patient having a resectable malignant tumor, then surgically resecting the tumor, is an effective method of treatment for a patient with a malignant tumor. In fact, Neefe et al. were unable to correlate natural killer cell activity and inhibition of tumor growth. See, Neefe et al., page 877, second column. Golub et al. did not find any correlation between natural killer activity and clinical benefit of the interferon. Five patients benefited from the interferon therapy while four patients had an increase in tumor growth during the therapy. In both groups, equivalent increases in natural killer cell activity were observed. See, Golub et al., pages 708-709. Thus, the combination of Markovic et al. and Golub et al., Toliou et al., or Neefe et al. does not render the presently claimed method of treatment obvious. The Examiner is requested to withdraw the rejection of claims 1, 7-8, 15-16, and 18-22 under 35 U.S.C. § 103.

The Examiner rejected claim 23 under 35 U.S.C. § 103(a) as being unpatentable over Markovic et al. (Clinical Immunology and Immunopathology, 60:181-189, 1991) in view of either Golub et al., Toliou et al., or Neefe et al. Markovic et al. were viewed as teaching that "anesthesia inhibits stimulation of natural killer cells in mice by interferon if the interferon is

administered after the anesthetic" and that "anesthesia induced inhibition of natural kill [sic] cell stimulation could mean that a surgical patient that is exposed to anesthesia is incapable of activating natural killer defenses in response to pathogenic insults which would lead to an increased susceptibility to post-operative infections."

The combination of Markovic et al. and Golub et al., Toliou et al., or Neefe et al. does not teach or suggest administering 4,000,000 U/m^2 per day or less of an α-interferon composition to a human prior to surgery. Markovic et al. indicate that natural killer cell activity induced with interferon prior to surgery is not altered by anesthesia. Markovic et al. do not teach or suggest that particular dosages of α-interferon (4,000,000 U/m^2 per day or less) are effective for preventing post-operative infections in humans. Golub et al., Toliou et al., and Neefe et al. are discussed above and also do not teach or suggest that particular dosages of α-interferon can be administered prior to surgery to prevent post-operative infection. In view of the above remarks, the Examiner is requested to withdraw the rejection of claim 23 under 35 U.S.C. § 103.

CONCLUSION

Applicant submits that all claims are in condition for allowance, which action is requested. The Examiner is invited to telephone the undersigned agent if it is felt that such would advance prosecution of the application.

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Respectfully submitted,

Date: 5/31/00

Monica McCormick Graham, Ph.D.
Reg. No. 42,600

CZH/das

Fish & Richardson P.C., P.A.
60 South Sixth Street, Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

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